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**Altered iPSC-derived neurons' sodium channel properties in subjects with Monge's disease.**

**Journal:** Neuroscience

**Publication Year:** 2015

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**PubMed link:** 25559931

**Funding Grants:** Developing a drug-screening system for Autism Spectrum Disorders using human neurons, A drug-screening platform for autism spectrum disorders using human astrocytes

**Public Summary:**

Here we report the use of stem cell technology to model Monge's disease in the lab. Our data revealed differences in the physiology of neurons that could be used in future drug screening platforms.

**Scientific Abstract:**

Monge's disease, also known as chronic mountain sickness (CMS), is a disease that potentially threatens more than 140 million highlanders during extended time living at high altitudes (over 2500m). The prevalence of CMS in Andeans is about 15-20%, suggesting that the majority of highlanders (non-CMS) are rather healthy at high altitudes; however, CMS subjects experience severe hypoxemia, erythrocytosis and many neurologic manifestations including migraine, headache, mental fatigue, confusion, and memory loss. The underlying mechanisms of CMS neuropathology are not well understood and no ideal treatment is available to prevent or cure CMS, except for phlebotomy. In the current study, we reprogrammed fibroblast cells from both CMS and non-CMS subjects' skin biopsies into the induced pluripotent stem cells (iPSCs), then differentiated into neurons and compared their neuronal properties. We discovered that CMS neurons were much less excitable (higher rheobase) than non-CMS neurons. This decreased excitability was not caused by differences in passive neuronal properties, but instead by a significantly lowered Na(+) channel current density and by a shift of the voltage-conductance curve in the depolarization direction. Our findings provide, for the first time, evidence of a neuronal abnormality in CMS subjects as compared to non-CMS subjects, hoping that such studies can pave the way to a better understanding of the neuropathology in CMS.

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